PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference DCDISPPCT154	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/US04/18642	International filing date *(day/month/year)* 09 June 2004 (09.06.2004)	Priority date *(day/month/year)* 09 June 2003 (09.06.2003)
International Patent Classification (IPC) or national classification and IPC IPC(7): B01L 3/02, 3/00, 11/00; G01N 21/00, 1/18, 1/10 and US Cl.: 422/100, 102, 103, 81; 436/180, 178; 73/863.72, 863.73, 863.84, 863.86		
Applicant DAKOCTOMATION DENMARK A/S		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *(sent to the applicant and to the International Bureau)* a total of ___ sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07 June 2005 (07.06.2005)	12 July 2005 (12.07.2005)
Name and mailing address of the IPEA/ US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Brian Gordon Telephone No. (571) 272-1700

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US04/18642

Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1(b))

☐ publication of the international application (under Rule 12.4)

☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☒ the description:
pages 1-23 as originally filed/furnished
pages* NONE received by this Authority on _____
pages* NONE received by this Authority on _____

☒ the claims:
pages 24-45 as originally filed/furnished
pages* NONE as amended (together with any statement) under Article 19
pages* NONE received by this Authority on _____
pages* NONE received by this Authority on _____

☒ the drawings:
pages 1-12 as originally filed/furnished
pages* NONE received by this Authority on _____
pages* NONE received by this Authority on _____

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing (*specify*): _____
☐ any table(s) related to the sequence listing (*specify*): _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing (*specify*): _____
☐ any table(s) related to the sequence listing (*specify*): _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims Please See Continuation Sheet	YES
	Claims Please See Continuation Sheet	NO
Inventive Step (IS)	Claims Please See Continuation Sheet	YES
	Claims Please See Continuation Sheet	NO
Industrial Applicability (IA)	Claims Please See Continuation Sheet	YES
	Claims Please See Continuation Sheet	NO

2. Citations and Explanations (Rule 70.7)
Please See Continuation Sheet

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

V.1. Reasoned Statements:
The opinion as to Novelty was positive (Yes)with respect to claims 4-5, 13, 15, 20, 22-30, 32-36, 48-49, 52-57, 60, 62-63, 66-67, 73, 75-76, 78-81, 103, 105, 113-118, 122-126, 133-137, 146, 150-151, 155-157, 160-163
The opinion as to Novelty was negative (No) with respect to claims Claims 1-3, 6-12, 14, 16-19, 21, 31, 37-47, 50-51, 58-59, 61, 64-65, 68-72, 74, 77, 82-102, 104, 106-1112, 119-121, 127-132, 138-145, 147-149, 152-154, 158-159, and 164-169
The opinion as to Inventive Step was positive (Yes)with respect to claims 4,5,13,15,20,22-30,32-36,48,49,52-57,60,62,63,66,67,73,75,76,78-81,103,105,113-118,122-126,133-137,146,150,151,155-157 and 160-163
The opinion as to Inventive Step was negative(NO) with respect to claims 1-3, 6-12, 14, 16-19, 21, 31, 37-47, 50-51, 58-59, 61, 64-65, 68-72, 74, 77, 82-102, 104, 106-1112, 119-121, 127-132, 138-145, 147-149, 152-154, 158-159, and 164-169
The opinion as to Industrial Applicability was positive (YES) with respect to claims 1-169
The opinion as to Industrial Applicability was negative(NO) with respect to claims NONE

Claims 2-3, 6-12, 14, 16-18, 21, 31, 37-46, 58-59, 61, 64-65, 68, 74, 82-89, 91-98, 106-109, 120-121, 127-131, 138-143, 148-149, 152, 158-159, and 164-169 lack novelty under PCT Article 33(2) as being anticipated by Singh et al. US 2002/0098122

Singh et al. disclose a microfabricated system for performing biochemical analysis on a test sample of substance. The system includes a substrate with a sample entry port, one or more pump chambers, and one or more mixers. Channels are connected between the pump chambers and the mixers to conduct the flow of the substance during the processing. A magnetic member is positioned on a diaphragm over each pump chamber, creating a pump that is actuated by attracting and repelling the magnetic member with a magnet. Each magnetic member is attracted or repelled independently of the other magnetic members.

Components involved in processes for conducting biological and chemical analysis include filters, valves, pumps, mixers, channels, reservoirs, and actuators.

The substrate can include other components, as required, depending on the processes to be performed. Such components can include one or more filters and/or reservoirs for storing reagents to be combined with the sample, and/or for depositing by-products from the processing.

One or more valves (called "check valves") can also be included to prevent backflow in the channels, e.g., during processing as the sample is combined with other substances and transported through the system. The check valves can be unidirectional or bidirectional, as required. One type of check valve that can be utilized includes a flap having one end movably attached to one sidewall of the channel while the other end of the flap is free to move with the force of the substance flowing against it.

Supplemental Box

The substrate can be fabricated from polymer materials that can be molded, embossed, and etched.

Biosensor device 102 provides signals to actuate valves, pumps, and mixers to control the flow and mixing of the sample and various reactants to and from reservoirs in microfluidic system 104.

FIGS. 3c and 3d show a cross-sectional side view and a top view, respectively, of a pump 320 that is suitable for use in microfluidic system 104 (FIG. 1). Pump 320 includes diaphragm 338 that causes alternating volumetric changes in a pump chamber 340 when deflected. When pump chamber 340 contains liquids or gases, they are transferred by the pumping action into another chamber or reservoir (not shown) via channels 342, 344 in substrate 346. Check valves 348, 350 are located in channels 342, 344, respectively, to control the flow of fluid into and out of chamber 340. The diaphragm 338 is actuated electro-magnetically with magnetic member 352 (plunger) being controlled by magnetic core 354 and alternating current in solenoid 356.

Techniques known in the art, such as silicon etching, plastic injection molding, and hot embossing can also be used to fabricate microfluidic system 104. A combination of fabrication methods well-known in the art can be used to fabricate flow channels 342, 344, pump chamber 340, and check valves 348, 350 in substrate 346.

In one embodiment, the top side of microfluidic system 104 includes channels 342, 344, and pump chamber 340. The top and bottom sides can include access holes 357, 367 for loading reagents and other substances into chamber 340, as required. The sample(s) and reagents can be introduced using a syringe and then access holes 357, 367 are sealed by chemically bonding layers 360, 362 to the top and/or bottom sides, respective.

Microfluidic system 104 can also be fabricated out of one or more layers of molded or embossed polymers. In one embodiment, channels, reservoirs, pump chambers, and check valves are embossed in substrate 346. A flexible layer is chemically bonded to the top of substrate 346, to form diaphragm 338 and seal the channels, reservoirs, and access holes on the top side. Magnetic members 352 for pumps 320 are positioned on top of the second layer. A top protective layer 360 and/or a bottom protective layer 362 can be included to seal and protect the top and bottom of substrate 346, as shown in FIG. 3c. The top protective layer 360 is flexible to allow movement of diaphragm 352 during actuation.

Diaphragm 338 is attached to the top of substrate 346 and is made out of a thin sheet of flexible material such as plastic, glass, silicon, elastomer, or any other suitable, flexible material. The flexibility or stiffness required of diaphragm 338 depends on the desired deflection of the diaphragm. Typically the stiffness is selected to achieve a total upward and downward deflection of approximately five to fifteen microns. Any suitable attachment mechanism, such as chemical bonding, can be used to attach diaphragm 338 to substrate 346. The bonding technique utilized should be capable of maintaining the seal while the pump 320 is operating.

Magnetic member 352 is made out of magnetic material which is attracted and repelled by a magnetic force from magnetic core 354. Magnetic member 352 can be adhesively bonded to diaphragm 338, or electroplated onto the diaphragm 338 during manufacturing. Substrate 346 can be made of plastic, silicon, or other suitable material that is capable of substantially retaining the shape of pump chamber 340 during operation.

An electrically conductive wire is coiled around magnetic core 354 to form solenoid 356. When an electric current passes through solenoid 356, a magnetic field is created in magnetic core 354. The polarity of the current can be alternated to change the direction of force of the magnetic field, thus alternately repelling and attracting magnetic member 352. The repelling and attracting forces cause diaphragm 338 to move, changing the volume of chamber 340. An increase in volume draws fluid or gas into chamber 340 via channel 342, and a decrease in volume forces the fluid or gas into channel 344. Applying a periodic excitation voltage to solenoid 356, such as provided by current source 364, causes diaphragm 338 to oscillate, producing a pumping action. The flow rate is thus directly controlled by the frequency of the alternating current to solenoid 356.

Check valve 348 controls the inflow of fluid or gas into chamber 340, and check valve 350

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controls flow out of chamber 340. Check valve 348 allows fluid to flow into chamber 340 when the volume of chamber 340 is increased, and prevents backflow of the fluid or gas when the volume of chamber 340 is decreased. Flow through channel 344 is controlled by check valve 350, which allows flow into channel 344 when the volume of chamber 340 is decreased, and prevents backflow from channel 344 when the volume of chamber 340 is increased.

Various types of check valves are suitable for use with the pump 320 to control the flow of fluid, gas, or other substance in the desired direction. In one embodiment, as shown in FIG. 3d, check valves 348 and 350 are passive flaps etched or molded in the substrate 346.

One way to mix very small amounts of two or more substances in microfluidic system 104 is to feed the flow streams into one channel as they are directed to a reservoir or pump chamber.

Claims 1-3, 6-12, 14, 16-18, 21, 31, 37-47, 50-51, 58-59, 64, 68-71, 74, 77, 82-102, 104, 106-112, 119-121, 127-132, 138-145, 147-149, 152-154, 158-159, and 164-169 lack novelty under PCT Article 33(2) as being anticipated by Karp US 6,644,944 B2.

Karp dicloses a microfluidic fluid control device can be used as a uni-directional valve within a microfluidic system. The invention also provides a microfluidic pump mechanism having two unidirectional valves separated by an expandable reservoir. Such devices may be formed in multiple layers and utilize flexible membranes.

In one separate aspect of the invention, a microfluidic fluid control device includes a first or inlet channel having a valve seat disposed therein at a valve region and a second or outlet channel with a flexible membrane separating the first channel and the second channel. The flexible membrane has an aperture aligned with the valve seat at a valve region. The aperture can be smaller than a seating surface of the valve seat. The flexible membrane can form a seal with the valve seat.

The microfluidic fluid control devices of the invention can be constructed to allow fluid flow in one direction, but substantially block fluid flow in the opposing direction. A microfluidic fluid control device may also include a second valve seat disposed in the second channel.

Microfluidic devices providing unidirectional flow control utility according to the invention may be fabricated in various ways using a wide variety of materials. For example, a computer-controlled plotter modified to accept a cutting blade may be used to cut various patterns through a material layer. Alternatively, a computer-controlled laser cutter may be used. As further alternatives, conventional stamping, cutting, and/or molding technologies may be employed to form stencil layers. The wide variety of materials that may be used to fabricate microfluidic devices using sandwiched stencil layers include polymeric, metallic, and/or composite materials, to name a few. Alternatively, microfluidic devices according to the present invention are fabricated from materials such as glass, silicon, silicon nitride, quartz, or similar materials.

The valve seat can be constructed from any suitable material or combination of materials. The valve seat may be formed as an integral part of one or more device layers or may be affixed to a surface of the device within a channel. In one embodiment, the valve seat is formed using single-sided adhesive tape material, or double-sided tape with a seating surface affixed to one side. The valve seat can also be formed as a raised portion of the substrate using fabrication techniques such as machining, molding, etching, or hot-pressing. The valve seat may also be formed by depositing a hardenable polymer onto a substrate. In a preferred embodiment, neither the sealing surface of the flexible membrane (the surface that will contact the valve seat) nor the sealing surface of the valve seat (the surface that will contact the flexible membrane) is an adhesive surface.

In FIG. 1C, fluid is injected through the outlet port 110, and passes through large vias 109 and 107 into the elongate channel 105. When the fluid reaches the aperture 108 in the membrane 102, the fluid contacts the valve seat 111. The aperture 108 is smaller than the diameter of the valve seat 111. Accordingly, since the membrane 102 defining the aperture rests upon the valve seat 111, the membrane 102 forms seals against the valve seat 111 and fluid passage in the direction of the valve seat 111 is blocked. In this particular example, if liquid is used as the working fluid, the liquid may not even reach the valve

seat 111, since as it is injected into the device 95, air within the channel 105, chamber region 105A, and large vias 107, 109 may be compressed ahead of the liquid front sufficiently to seal the membrane 102 against the valve seat 111, thus providing a trapped air pocket ahead of the liquid front. An important note is that even drastically increasing the pressure in this example will not cause leakage through the valve, because pressure introduced to the device through the outlet port 110 it simply forces the membrane 102 adjacent to the chamber regions 105A, 106A into tighter contact against the valve seat 111.

FIG. 1D provides a second example of operation of the device 95, in which fluid is injected into the inlet port 112. From the inlet port, the fluid passes into the channel segment 106 and the enlarged chamber region 106A. In this example, as the fluid pressure is increased, stencil layer 102 can be deformed upward into the chamber region 105A, since the membrane 102 is constructed from a flexible material, which in this case is 0.002" (50 microns) thick PET. Upward deformation of the membrane 102 opens a flow path that permits fluid in the chamber 106A to flow through the aperture 108, through the chamber 105A and channel 105, and ultimately to the outlet port 110.

Microfluidic fluid control structures also can be combined in devices to create more complex fluidic devices. For instance, multiple devices can be combined in serial or in parallel. In one example, two microfluidic control regions can be combined in series to form a pump mechanism. The pump mechanism has two unidirectional valves arranged such that their flow directions are aligned. The two unidirectional valves are separated by an expandable reservoir area. The expandable reservoir area can be any substantially sealed reservoir having a changeable volume. As will be appreciated by one skilled in the art, a wide variety of variable-volume reservoir devices may be provided. For example, in one embodiment the expandable reservoir may include a piston/cylinder assembly. In another embodiment, the expandable reservoir may include a deformable pump membrane, the deformation of which changes the volume of the expandable reservoir. Expanding the pump membrane to enlarge the reservoir draws fluid in through one valve, while tightly sealing the other valve. Contracting the membrane to compress the reservoir then seals the input valve, and the fluid flows through the outlet valve.

A pump mechanism may also include an actuator for moving the deformable pump membrane. The actuator may be physically attached to the deformable membrane by way of a structure such as, for example, a piston (plunger), lever, solenoid, etc.

In yet another embodiment, a microfluidic unidirectional flow device may be provided with valve seats in both the inlet and outlet channels adjacent to an aperture in a central membrane. As shown in FIG. 4, a first channel 158 has a valve seat 180 disposed in a valve region below an aperture 160 defined in a central membrane 152. Flexible membrane 152 has an aperture 160 aligned with both a first valve seat 180 and a second valve seat 181. In operation, fluid flows was initiated in the inlet channel 158. At a sufficient pressure, the flexible membrane 152 was deflected towards the outlet channel 156, permitting fluid to flow from the first channel 158 to the second channel 156. As the pressure was increased, the flexible membrane 152 adjacent to the aperture 160 was deformed further upward until it contacted the second valve seat 181, thus restricting further fluid flow. This device effectively creates a window of operating pressure within a device, only allowing fluid flow when a minimum pressure is reached and restricting fluid flow again when a higher pressure is attained.

Claims 4-5, 13, 15, 20, 22-30, 32-36, 48-49, 52-57, 60, 62-63, 66-67, 73, 75-76, 78-81, 103, 105, 113-118, 122-126, 133-137, 146, 150-151, 155-157, and 160-163 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest a liquid flow deflection element comprising a vertical flow element below said reservoir and a horizontal flow element next to said metering chamber, collapsible molded reservoir in the structure of a bottle, an interchangeable reservoir, dual clamp element, biological sample located directly below said liquid exit element, an automated biological staining device, an internal diaphragm compressor, repeatable liquid measurement device, internal mechanical stop, uncompression spring element, manual compression element, unidirection valve, including a valve disk, valve retainer, and valve membrane; a seal selected from the group consisting of a radial o-ring and flange o-ring; reservoir housing around said reservoir; a reduced friction dispenser, a self priming element, tip-down piming element, and a shipping lock.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Supplemental Box

Claims 1-169 meet the criteria set out in PCT Article 33(4), and thus meet industrial applicability because the subject matter claimed can be made or used in industry.

---------- NEW CITATIONS ----------